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Review Article

Applications of Hydrogels in the Treatment of Hepatocellular Carcinoma

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Abstract

Hepatocellular carcinoma (HCC) is among the most lethal malignant tumors worldwide. Current treatment options are still limited due to not-selective action and therapy resistance. Hydrogels are water-insoluble, hydrophilic, cross-linked, three-dimensional networks of polymer chains having the ability to swell and absorb water but do not dissolve in it. Hydrogels are highly biocompatible and have properties similar to human tissues that make it suitable to be used in various biomedical applications, including drug delivery and tissue engineering. The role of hydrogels in the therapy of HCC is highly emerging in recent years. In this review, we highlighted important characteristics of hydrogels and the application of hydrogels of pioneering strategies for the treatment of hepatocellular carcinoma is also discussed.

Keywords: *Hepatocellular carcinoma, Hydrogels, Tumor therapy, Drug delivery system*

Introduction

Hepatocellular carcinoma (HCC) is a primary liver cancer that usually develops in patients with an underlying liver disease and sustained chronic liver damage [1]. It is among the most prevalent and lethal tumors worldwide, ranking fifth and third in terms of global incidence and mortality of all cancers [2]. In 2020, almost 906,000 new cases and 830,000 deaths has been reported for liver cancer globally with more than 80% of these from HCC [3]. Current treatments of HCC include surgery, ablation, chemotherapy, targeted therapy and immunotherapy [4, 5]. In spite of favorable results observed in some patients with early HCC [6], treatment remains challenging in the advanced disease [7]. The non-selective action of tumor therapy can result in severe side effects which seriously compromise patients' benefits. Primary or secondary therapy resistance is as well a serious drawback that impedes patients clinical outcomes [8]. Therefore, new formulations are under research and development to improve the efficacy of current anti-cancer therapeutics. In this regard, hydrogels represents a promising strategy [9].

Injectable in-situ-forming hydrogels have received considerable attention due to their outstanding properties, such as excellent biocompatibility, facile preparation and high biodegradability making them excellent candidates for biomedical applications [10]. Hydrogels have recently gained special attention due to their potential to allow in situ sustained and controlled anti-tumor drug release. In particular, stimuli-responsive hydrogels which are able to change their physical state from liquid to gel accordingly to external factors such as temperature, pH, light, ionic strength, and magnetic field, among others. Some of these formulations presented promising results for the treatment and recurrence prevention of HCC. The present review aims to summarize the main properties and application of hydrogels in HCC treatment [11].

1. Difficulties in the treatment of HCC

HCC is a highly heterogeneous malignance. A variety of pathogenic factors and oncogene activation drive the occurrence and development of HCC [12]. Numerous studies have attempted to reveal the molecular characteristics of liver cancer, but it is still not able to guide the precise treatment in clinical practice [13-15].

Accumulating evidence suggests that a suppressive tumor microenvironment (TME) represents a major obstacle in the optimal treatment of HCC [16]. Besides cytotoxic lymphocytes (CTL) and natural killer cells (NK) that are generally considered to be effective anti-tumor immune cells, TME contains a wide range of other cells that are involved in the cross-talk with anti-tumor immune cells, including cancer-associated fibroblasts (CAF), endothelial cells, and tumor-associated macrophages [17-20]. CAFs are key drivers of extra cell matrix (ECM) remodeling and the major source of TGF-β protein family that is involved in the immune-excluded TME in HCC [21, 22]. This excessive deposition of ECM also alters the biomechanical properties of the diseased liver, leading to increased liver stiffness, which can enhance tumor growth, limits drug diffusion and efficiency[23, 24]. TME is also characterized by an abnormal vascular network, with increased interstitial fluid pressure (IFP), heterogeneous leakiness, uneven blood flow distribution, and abundant tumor-related stromal cells [25]. These factors can affect drug transport and limit drug effectiveness to various extents [26]. Following intravascular administration, the tortuous tumour vasculature may present a primary barrier for therapies like transcatheter arterial chemoembolization (TACE) or chimeric antigen receptor T-cell (CAR-T) from the vascular compartment to the tumor site [23].

In addition, the biological characteristics of HCC may evolve with the progress of treatment. Anti-angiogenic therapy or TACE can lead to hypoxia of TME, which may alter the complex cellular metabolism, induce secondary resistance and even promote tumor recurrence [27, 28]. Tissue damage caused by tumor resection or liver transplantation can promote the release of damage associated molecular patterns (DAMPs) and various cytokines, which could promote the chronic inflammation on the surgical site and lead to tumor recurrence [29].

Therefore, tumor heterogeneity, complexity of TME and tumor recurrence remain difficulties in the treatment of HCC. In order to solve these problems, we need to develop more advanced drug delivery systems (DDS) and more reliable prediction models based on the characteristics of HCC.

2. Characteristics of hydrogels

2.1 Good biocompatibility

Hydrogels, which are defined as two- or multi-component systems composing of a three-dimensional network of cross-linked hydrophilic polymer chains, are one of the most full-fledged biomaterials nowadays [30]. Because their structures are very similar to the natural ECM, hydrogels such as collagen, agarose and polyethylene glycol, are established to have a good biocompatibility [31, 32]. And that factor allows them to maintain cellular homeostasis and improve many cellular functions *in vivo* and merely cause inflammatory responses [33-35]. With the advantages of colorlessness, odourlessness and non-toxicity, hydrogels are undoubtedly becoming the optimal three-dimensional (3D) cell culture platforms and facilitate cell encapsulation and expansion *in vitro* and *in vivo* for efficient tissue regeneration and cancer therapy [36, 37].

2.2 High biodegradability

Hydrogels have a high controllable biodegradability without production of toxic substances after the degradation. For example, fibrin hydrogel can be totally degraded and absorbed under physiological conditions, which is significant for the usage and safety of hydrogel [38]. The degradation mechanisms of hydrogel, mainly attribute to the fracture of polymer molecular chains, including dissolution by erosion, hydrolysis, hydrolysis after dissolution, enzymatic hydrolysis [39, 40]. Therefore, it's adjustable and biologic for hydrogels to degrade in different situations. Hydrogels that are sensitive to the environmental stimuli have great potential to be used in drug delivery to specific sites in human body [41]. Compared with traditional systemic administration methods which may lead to side effects and low bioavailability, hydrogels are more effective controllable, and local aggregation of drugs is more tolerable as well. In addition, biodegradable hydrogels can largely avoid intense immune rejection and systemic organ toxicity. These characteristics suggest that hydrogels can open up an effective way to develop environmental responsive and effective biomaterials in the field of cancer therapy [42].

2.3 Outstanding permeability

Due to the composition of hydrophilic polymer chains, hydrogels possess an outstanding permeability to water-soluble substances, the characteristic of the water in a hydrogel can control the overall permeability of substance into and out of the gel [43].

With high water absorbing/holding capability and soft tissue-like physicochemical properties, hydrogels can easily absorb and transport large amounts of water, oxygen, nutrients, drugs and other water-soluble materials, while themselves remain stable and insoluble in water due to the 3D network [44, 45]. With low selective permeability to proteins, hydrogels are able to protect macromolecular materials from unnecessary degradation and are sufficiently capable of drug encapsulation [46]. Through control on swelling and degradation depending on different application needs, hydrogels are applicable drug carriers with large loading capacity, which represents increasing the advantages for future drug therapy and reducing risks to the patients from some drug use. For substance, photopolymerized hydrogels, hydrogel materials formed through photopolymerization processes, have been designed to be used as drug delivery systems for the past few years [47].

Furthermore, although the mechanical characteristics of hydrogels are weaker compared to their biological characteristics, the development of new hydrogels in various ways such as nanoparticles-hydrogel, can greatly improve their mechanical properties, combined with more excellent biological performance, which leads to their more extensive and suitable application in the field of biomedicine [48].

3. Applications of hydrogels in the treatment of HCC

Hydrogels offer an attractive solution in reaching a sustained and targeted release of pharmaceuticals, both increasing the effect of the drug and lowering side effects [49]. These advantages make hydrogels an ideal class of biomedical materials for drug delivery, biosensing and *in vitro* tumor tissue engineering [50-52]. The applications of hydrogels in the treatment of HCC are summarized in Fig 1.

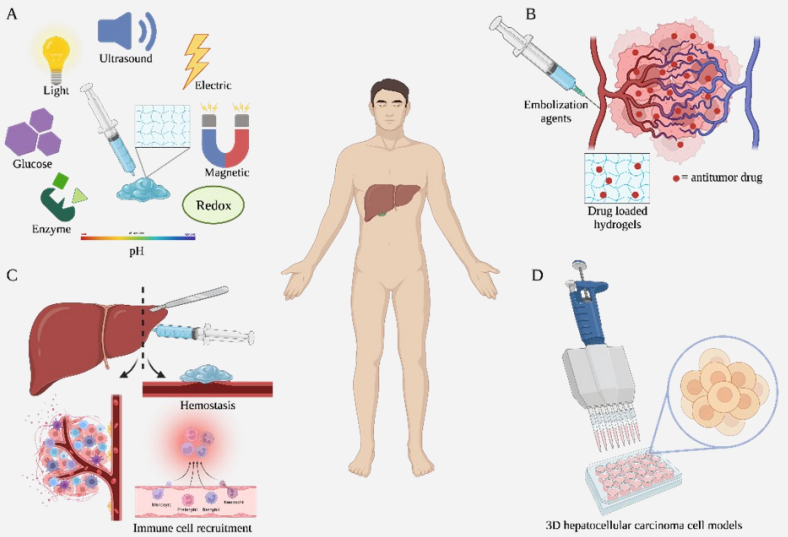

Figure 1: *Hydrogels-based HCC treatment strategies can be roughly divided into those: (A) Control of hydrogel properties in response to environmental stimuli; (B) Optimize the precise delivery of drugs in tumors; (C) Activating anti-tumor immune response to prevent tumor recurrence; (D) Personalized prediction of drug efficacy via the constructing in vitro HCC models.*

3.1 Hydrogels as stimuli-responsive drug delivery carriers

TACE represent a classical locoregional chemotherapy performed via a percutaneously inserted intravascular catheter, which reaches as close as possible to the tumor region to create a hot spot with the cytotoxic drugs. According to current guidelines, TACE is the recommended as first-line therapy for patients with early/intermediate HCC or as a bridge to liver transplantation [5, 53-55]. Key processes related to a success TACE are mass transport across the vascular barrier, penetration through tumor parenchyma and appropriate drug release. Injectable hydrogel with environment responsive ability had been successfully applied in TACE procedure for HCC treatment.

Physical crosslinking hydrogels with stimulus responsiveness were popular design as TACE reagents. Nguyen and colleagues successfully synthesized an amphiphilic anionic PCLA-PUSSM copolymer made of poly(ethylene glycol) (PEG), poly(ε-caprolactone-co-lactide) (PCLA), and poly(urethane sulfide sulfamethazine) (PUSSM) [56]. The PCLA-PUSSM copolymer solution remained liquid status at pH 8.5 and rapidly became solid upon pH decrease. Animal model evaluation revealed that this PCLA-PUSSM hydrogel could effectively perform the chemoembolization effect and release doxorubicin (DOX) in a sustained manner to inhibit the tumor growth.

Yan et al. also reported an *in situ* formed magnetic hydrogel with thermal-responsiveness, strong adhesion in wet conditions, high magnetic hyperthermia, and biocompatibility, leading to efficient TACE treatment [57]. This hydrogel could completely embolize tumor arterial vessels in animal models, which could serve as responsive materials to external magnetic field and body temperature for HCC treatment.

In short, injectable hydrogel with environment responsive ability had been successfully applied in TACE procedure for hepatocellular cancer (HCC) treatment in an animal model, and it exhibited the ability to stably maintain high drug concentration at the tumor site. Hence, the design of biocompatible and biodegradable polymeric hydrogels might serve as a practical TACE agents, which could be further combined with a wide spectrum of chemotherapeutics.

3.2 Hydrogels as prevention of tumor recurrence

Prevention of tumor recurrence is a major clinical challenge for patients with HCC after operation. While adjuvant therapies such as targeted therapy and chemotherapy can benefit some patients, most patients with HCC will experience tumor recurrence or metastasis after surgery. Growing interests have promoted the development of implantable hydrogels systems for locoregional treatment, since they load and controllably release therapeutic agents with high bioavailability and low systemic toxicity.

For example, Dang and colleagues developed a 3D printed Gel-SA-CuO hydrogel scaffolds that could efficiently inhibit postoperative HCC recurrence [58]. During the biodegradation of hydrogel scaffolds in the resection site, CuO nanoparticles can be sustained released, which not only function as the resource of Cu^{2+} to produce intracellular reactive oxygen species (ROS) but also serve as photothermal agent to generate heat. Additionally, ferroptosis of residual tumor cells can be induced through Cu^{2+}-mediated GSH depletion [58].

Hydrogel-based delivery systems can also perform as adjuvant for optimal current immune therapy. In a recent report, researchers have developed a biocompatible hydrogel with tumor acidity neutralizer and NETs lyase that could enhance NK cell infusion to prevent recurrence post-surgery [59]. The hydrogel can be injected to surgical margin and neutralizes tumor acidity to reduce tumor infiltration of immunosuppressive cells, and releases DNase I in a pH-responsive manner to degrade NETs. These effects jointly enhanced NK cell infusion and prevent against HCC recurrence [59]. Another novel hydrogel delivery system mainly loaded with tumor-specific neoantigen, toll-like receptor 9 agonist and stimulator of interferon genes agonist can elicit robust anti-tumor immunity when combined with TIM-3 blockade [60]. Unlike injection of other stimulators with only short-term immune protection, this neoantigen loaded-gels evoke significant immune protection to prevent pulmonary metastasis in HCC and establish long-term memory against tumor re-challenge.

Overall, these studies provide attractive and promising synergistic strategies for HCC immunotherapy with possible clinical translation prospects. They may pave the way for the development of advanced multifunctional implantable platform for eliminating postoperative re-lapsable cancers like HCC.

3.3 Hydrogel-aided tumor models as predictive therapeutic evaluation

There is an urgent need for improved preclinical models for the development of HCC-targeted therapies. Tumor spheroids are cellular microspheres obtained in cell culture which have become largely used in cancer research [61, 62]. In order to improve the reliability of the results obtained with the spheroid models, many 3D cultures of liver cancer cells are availing themselves of hydrogels based on collagen, alginate, gelatin or containing growth factors immobilized in the structure via different chemical processes [63-66]. Within hydrogel structures, spheroidal masses are formed under non-adherence conditions, which can mimic the characteristics of TME in terms of ECM secretion, hypoxia, cellular interaction, gradients diffusion and increased resistance to treatments in the experimental settings [67].

Researchers have designed 3D biomimetic HCC models with tumor and physiologically relevant hydrogels such as collagen and fibrinogen to mimic the bio-physical properties of TME[68, 69]. The results of these studies indicate that the formation of hetero-spheroids model is more representative of the *in vivo* situation compared to traditional 2D cultures with decreased response to chemotherapy, mimicking drug resistance typically seen in real HCC patients [68, 69]. Hypoxia-induced cell death has been found in the *in vivo* tumor environment in which the cells are deprived of oxygen and modify their behavior by developing a more aggressive phenotype. The phenomena of cellular necrosis due to hypoxia in hydrogels-based spheroids can be induced in some cases [70]. In other studies, researchers also used alginate hydrogels to reveal the possible cellular and molecular mechanisms that preside over the development of HCC metastases [63]. The results showed that the cells reached an increased maturity in the alginate hydrogel–based spheroids with respect to the monolayers, especially for cells retaining high metastatic potential, thus suggesting that this alginate hydrogel is able to structurally and functionally mimic the pro-metastases HCC TME [63, 71].

Patient-derived organoids have been shown to closely recapitulate human tumor biology and are becoming tool for personalized biomarker identification and drug screening, owing to their ability to reflect the genetic complexity of the primary tumor [72]. It has been shown that liver or pancreatic cancer cells can grow in the form of organoids inside ECM-based gel as a natural biomaterial [73]. Fong et al. engineered *in vitro* conditions conducive for the culture of HCC organoids derived from a panel of 14 different HCC-PDX lines through the use of a 3D macroporous cellulosic sponge system. Their results demonstrate the feasibility of using these in vitro HCC-PDX models for drug testing, paving the way for more efficient preclinical studies in HCC drug development [74].

Collectively, these findings highlighted the key role played by biomaterials, synthetic and biological hydrogels in the establishment of HCC spheroids and organoids, which is helpful for preclinical research and clinical drug screening.

Conclusions

HCC is one of the most common and fatal malignant tumors. Its high heterogeneity, inhibitory TME and common tumor recurrence bring great difficulties in the clinical settings. However, the emergence of hydrogels has brought new hope to the clinical treatment of HCC. As biocompatible materials with outstanding permeability and high environmental responsiveness, they not only improve the efficacy of existing chemotherapy and immunotherapy, but also serve as an effective preclinical HCC model that can help clinical scientists to explore the potential mechanisms and intervention of malignant behavior of HCC.

Conflict of interest

The authors declare no conflict of interest. Figures were created with BioRender software.

Author's contributions

Gechun Wang collected the related papers and drafted the manuscript; Xuqiu Shen drafted the figures; Kexin Jiang, Yihan Chai and Lichan Pan revised the manuscript and provided advice to the manuscript; Qi Chen, Zhengze Huang and Yuelong Liang participated in the design of the review and drafted the manuscript. All authors read and approved the final manuscript.

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